COVID-19 Therapeutics: Oral Antivirals

MISSISSIPPI STATE DEPARTMENT OF HEALTH
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Oral Antivirals

- **Paxlovid**: Nirmatrelvir + Ritonavir
  - Nirmatrelvir - a SARS-CoV-2 main protease inhibitor
  - Ritonavir - a CYP3A inhibitor included to increase nirmatrelvir plasma levels
    - Ritonavir alone has no activity against SARS-CoV-2

- **Molnupiravir** – a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis

EUA- Authorized Use

Paxlovid:

- Treatment of mild-to-moderate COVID-19
- Adults and pediatric patients (12 years of age and older weighing at least 40 kg)
- Positive results of direct SARS-CoV-2 viral testing
- High risk for progression to severe COVID-19, including hospitalization or death
  - [People with Certain Medical Conditions | CDC](#)
- Must be started within 5 days of symptom onset
- EUA: [FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR PAXLOVID (fda.gov)](#)

EUA- Authorized Use

Molnupiravir:

- Treatment of mild-to-moderate COVID-19
- Adults (**18** years of age and older)
- Positive results of direct SARS-CoV-2 viral testing
- High risk for progression to severe COVID-19, including hospitalization or death
  - [People with Certain Medical Conditions | CDC](#)
- Alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate
- Must be started within 5 days of symptom onset
- EUA: [FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR MOLNUPIRAVIR (fda.gov)](#)

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Limitations of Authorized Use

Paxlovid and molnupiravir are not authorized for:
- Initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19
- Use as pre-exposure or post-exposure prophylaxis for COVID-19
- Use for longer than 5 consecutive days

Efficacy In Clinical Trials

- **Paxlovid:**
  - EPIC-HR: [EPIC-HR: Study of Oral PF-07321332/Ritonavir Compared With Placebo in Nonhospitalized High Risk Adults With COVID-19 - Full Text View - ClinicalTrials.gov](#)
  - Reduced COVID-19 related hospitalization and death by 88% when given within 5 days of symptom onset

- **Molnupiravir:**
  - Trial P002 (MOVe-OUT): [Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482-002) - Full Text View - ClinicalTrials.gov](#)
  - Reduced COVID-19 related hospitalization and death by 30% when given within 5 days of symptom onset

Prescribing Requirements

- Paxlovid and molnupiravir require a prescription
- Prescribers must have an encounter with the patient prior to issuing a prescription
  - May be an in-person or virtual encounter
- Include the date of symptom onset on the prescription
  - Must be filled within 5 days of symptom onset
- Patients must be given a copy of the "Fact Sheet for Patients, Parents, and Caregivers"
  - Paxlovid: https://www.fda.gov/media/155051/download
  - Molnupiravir: https://www.fda.gov/media/155055/download

Dosing

- Begin treatment as soon as possible after COVID-19 diagnosis and within 5 days of symptom onset

- **Paxlovid**
  - Two 150 mg tablets (300 mg) nirmatrelvir with one 100 mg tablet ritonavir orally twice daily for 5 days
  - May be taken with or without food
  - Dose reduction needed for moderate renal impairment

- **Molnupiravir**
  - Four 200 mg capsules (800 mg) taken every 12 hours for 5 days
  - May be taken with or without food

Safety

Paxlovid:
- Adverse events (incidence ≥1%)
  - dysgeusia (6%)
  - diarrhea (3%)
  - hypertension (1%)
  - myalgia (1%)

Molnupiravir:
- Adverse events (incidence ≥1%)
  - diarrhea (2%)
  - nausea (1%)
  - dizziness (1%)

Drug Interactions: Paxlovid

Prescribe alternative COVID-19 therapy for patients receiving any of the following:	
Amiodarone	Propafenone
Carbamazepine	Ranolazine
Clopidogrel	Rifampin
Clozapine	Rivaroxaban
Dofetilide	Sildenafil for pulmonary HTN
Flecainide	St. John's wort
Phenobarbitol	Tadalafil for pulmonary HTN
Phenytoin	Ticagrelor

For full list of contraindications see: Statement on Paxlovid Drug-Drug Interactions | COVID-19 Treatment Guidelines (nih.gov)

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Drug Interactions: Paxlovid

If withholding any of the following medications is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy:	
Benzodiazepines:	Alprazolam, Clonazepam, Diazepam, Triazolam
Erectile dysfunction:	Sildenafil, Tadalafil, Vardenafil
Pain:	Codeine, Fentanyl, Hydrocodone, Meperidine, Oxycodone, Tramadol
Prostate:	Alfuzosin, Silodosin, Tamsulosin
Statins:	Atorvastatin, Lovastatin, Rosuvastatin, Simvastatin

For full list see: Statement on Paxlovid Drug-Drug Interactions | COVID-19 Treatment Guidelines (nih.gov)

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Drug Interactions: Molnupiravir

- No drug interactions have been identified based on the limited data available

Special Populations: Renal Impairment

Paxlovid:

eGFR	PAXLOVID Dose
>60 mL/min (normal renal function or mild renal impairment)	300 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days
≥30 to ≤60 mL/min (moderate renal impairment)	150 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for 5 days
<30 mL/min (severe renal impairment)	Not recommended

- Pharmacists need to remove any unneeded tablets and dispose of per the site's standard policy
- Instructions for pharmacists and sticker packs accompany each shipment of Paxlovid

Molnupiravir:
- No adjustment is recommended in patients with any degree of renal impairment

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Special Populations: Pregnancy

Paxlovid
- No available clinical data on pregnancy or with breast feeding
- Animal studies showed reduced body weights at ~10x the nirmatrelvir exposure seen in humans with the authorized dose

Molnupiravir
- Not recommended for use during pregnancy
- Authorized for use in pregnancy only if benefits would outweigh risks for the individual patient
  - Documentation requirements apply

Family Planning Considerations

Paxlovid
- Ritonavir may reduce efficacy of combined hormonal contraceptives
  - Patients should use an effective alternative contraceptive method or an additional barrier method of contraception

Molnupiravir
- Females of childbearing potential should be advised of potential risk to fetus
  - Alternate method of contraception should be used for the duration of the treatment and for <u>4 days</u> after the last dose
- Males of reproductive potential who are sexually active with women of childbearing potential should use a reliable method of contraception during treatment and for at least <u>3 months</u> after the last dose

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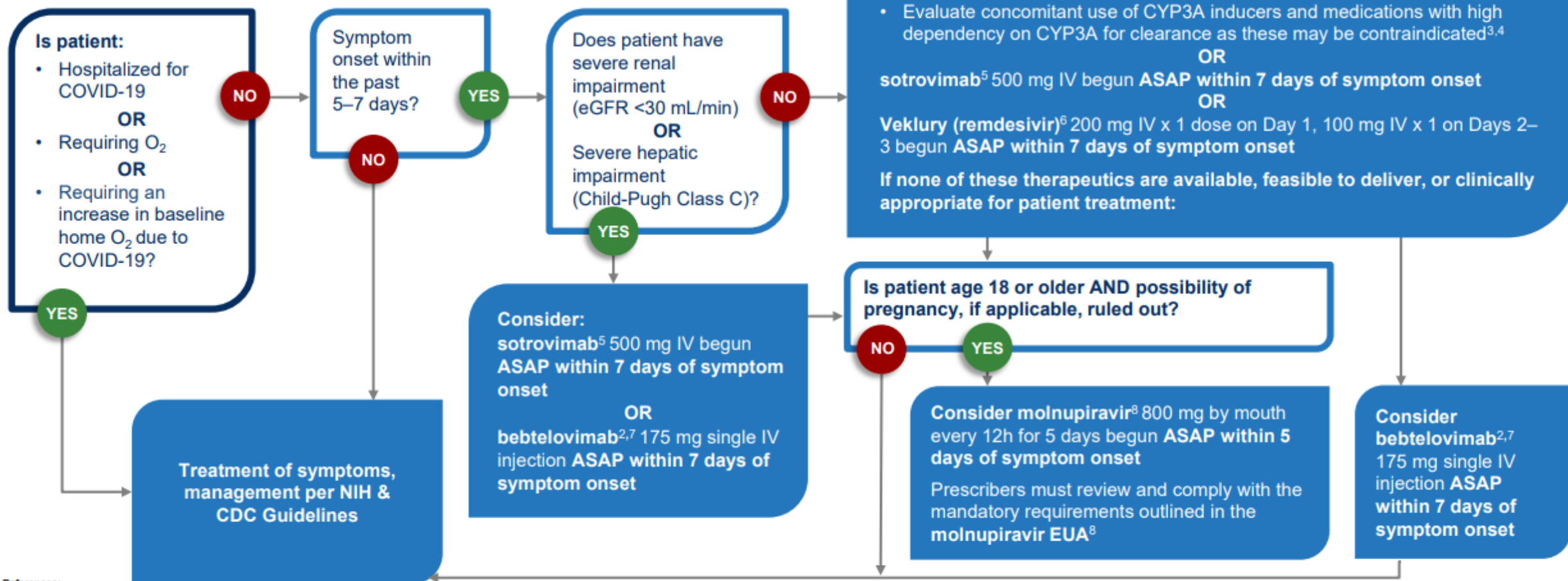STATE DEPARTMENT OF HEALTH

Clinical Decision Tool

- [Adult or pediatric (age 12 and older and weight 40kg or greater) with mild to moderate COVID-19 & high risk for progression to severe disease (phe.gov)](phe.gov)

COVID-19 Outpatient Therapeutics
Clinical Decision Aid for Ages 12+

Adult or pediatric patient (ages 12 and older weighing at least 40 kg) with mild to moderate COVID-19 and at high risk for progression to severe disease

Is patient:
- Hospitalized for COVID-19

  OR
- Requiring O_2

  OR
- Requiring an increase in baseline home O_2 due to COVID-19?

NO →

Symptom onset within the past 5–7 days?

YES →

NO

Does patient have severe renal impairment (eGFR <30 mL/min)

OR

Severe hepatic impairment (Child-Pugh Class C)?

NO →

YES

YES

Treatment of symptoms, management per NIH & CDC Guidelines

Consider:
sotrovimab[5] 500 mg IV begun **ASAP within 7 days of symptom onset**

OR

bebtelovimab[2,7] 175 mg single IV injection **ASAP within 7 days of symptom onset**

Consider one of the following therapeutics, if available[1,2]:

Paxlovid[3] within 5 days of symptom onset
- **eGFR ≥ 60 mL/min:** 300 mg nirmatrelvir taken with 100 mg ritonavir twice daily for 5 days
- **eGFR ≥ 30 to < 60:** 150 mg nirmatrelvir taken together with 100 mg ritonavir twice daily for 5 days
- Evaluate concomitant use of CYP3A inducers and medications with high dependency on CYP3A for clearance as these may be contraindicated[3,4]

OR

sotrovimab[5] 500 mg IV begun **ASAP within 7 days of symptom onset**

OR

Veklury (remdesivir)[6] 200 mg IV x 1 dose on Day 1, 100 mg IV x 1 on Days 2–3 begun **ASAP within 7 days of symptom onset**

If none of these therapeutics are available, feasible to deliver, or clinically appropriate for patient treatment:

Is patient age 18 or older AND possibility of pregnancy, if applicable, ruled out?

NO

YES

Consider molnupiravir[8] 800 mg by mouth every 12h for 5 days begun **ASAP within 5 days of symptom onset**

Prescribers must review and comply with the mandatory requirements outlined in the **molnupiravir EUA**[8]

Consider bebtelovimab[2,7] 175 mg single IV injection **ASAP within 7 days of symptom onset**

References:
[1] NIH's COVID-19 Treatment Guidelines Therapeutic Management of Nonhospitalized Adults With COVID-19. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/
[2] NIH's COVID-19 Treatment Guidelines Statement on bebtelovimab https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-bebtelovimab/?utm_source=site&utm_medium=home&utm_campaign=highlights
[3] Paxlovid EUA. https://www.fda.gov/media/155050/download
[4] NIH's COVID-19 Treatment Guidelines Panel's Statement on Potential Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-paxlovid-drug-drug-interactions/
[5] Sotrovimab EUA. https://www.fda.gov/media/149534/download
[6] Veklury (remdesivir) Prescribing Information. https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf
[7] Bebtelovimab EUA. https://www.fda.gov/media/156152/download
[8] Molnupiravir EUA. https://www.fda.gov/media/155054/download

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Therapeutic Locator

- Sites which dispense oral antivirals can be found on the MSDH website:
  - [MS COVID-19 Therapeutics Locator](#) (Interactive map)
  - [MS Pharmacies That Dispense Oral Antivirals](#) (PDF)

Resources

- Fact Sheets for Healthcare Providers:
  - Paxlovid: https://www.fda.gov/media/155050/download
  - Molnupiravir: https://www.fda.gov/media/155054/download
- CDC – People with certain medical conditions: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
- What Clinicians Need to Know About the New Oral Antiviral Medications for COVID-19 (cdc.gov)
- Side-by-Side Overview of Outpatient Therapies Authorized for Treatment of Mild-Moderate COVID-19: https://www.phe.gov/emergency/events/COVID19/therapeutics/Documents/side-by-side-overview.pdf

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